PATENT COOPERATION TREATY

	From the INTERNATIONAL BUREAU
PCT	То:
NOTIFICATION OF ELECTION (PCT Rule 61.2)	United States Patent and Trademark Office (Box PCT) Crystal Plaza 2 Washington, DC 20231 ÉTATS-UNIS D'AMÉRIQUE
Date of mailing (day/month/year)	
26_February 1999 (26.02.99)	in its capacity as elected Office
International application No. PCT/JP98/02613	Applicant's or agent's file reference PWO-17050
International filing date (day/month/year)	Priority date (day/month/year)
15 June 1998 (15.06.98)	17 June 1997 (17.06.97)
Applicant	
MIYAKE, Hiroshi et al	
The designated Office is hereby notified of its election made. In the demand filed with the International Preliminary O2 December in a notice effecting later election filed with the International Preliminary O2 December was was was not made before the expiration of 19 months from the priority of Rule 32.2(b).	Examining Authority on: 1998 (02.12.98) national Bureau on:
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer K. Takeda

2497084

Telephone No.: (41-22) 338.83.38

Facsimile No.: (41-22) 740.14.35

PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

SEKI, Hideo Fujisawa Pharmaceutical Co., Ltd. Osaka Factory 1-6, Kashima 2-chome Yodogawa-ku, Osaka-shi Osaka 532-8514 **JAPON**

IMPORTANT NOTIFICATION
International filing date (day/month/year) 15 June 1998 (15.06.98)
Priority date (day/month/year) 17 June 1997 (17.06.97)

FUJISAWA PHARMACEUTICAL CO., LTD. et al

- 1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- 2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- 3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date

Priority application No.

Country or regional Office or PCT receiving Office

Date of receipt of priority document

17 June 1997 (17.06.97)

PO7359

AU

17 July 1998 (17.07.98)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

Sean Taylor

Telephone No. (41-22) 338.83.38

Facsimile No. (41-22) 740.14.35

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

l To:

SEKI, Hideo Fujisawa Pharmaceutical Co., Ltd. Osaka Factory 1-6, Kashima 2-chome Yodogawa-ku, Osaka-shi Osaka 532-8514 JAPON

Date of mailing (day/month/year)

23 December 1998 (23.12.98)

Applicant's or agent's file reference

PWO-17050

IMPORTANT NOTICE

International application No. PCT/JP98/02613

International filing date (day/month/year)
15 June 1998 (15.06.98)

Priority date (day/month/year) 17 June 1997 (17.06.97)

Applicant

FUJISAWA PHARMACEUTICAL CO., LTD. et al

 Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice: AU,BR,CA,CN,EP,IL,JP,KR,PL,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AL,AM,AP,AT,AZ,BA,BB,BG,BY,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GE,HU,IS,KE,KG,KZ,LC,LK, LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PT,RO,RU,SD,SE,SG,SI,SK,TJ,TM,TR,TT,UA, UG,UZ,VN

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

 Enclosed with this Notice is a copy of the international application as published by the International Bureau on 23 December 1998 (23.12.98) under No. WO 98/57954

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Authorized officer

J. Zahra

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.83.38

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PCT/JP98/02613

Continuation of Form PCT/IB/308

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year) 23 December 1998 (23.12.98)	IMPORTANT NOTICE
Applicant's or agent's file reference PWO-17050	International application No. PCT/JP98/02613

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT.

(PCT Article 36 and Rule 70)



Applicant's or ac		file reference	FOR FURTHER ACTION	See Notifica ON Preliminary	ation of Transmittal of International Examination Report (Form PCT/IPEA/416)
PWO-17050			International filing date (day/	month/vear)	Priority date (day/month/year)
International app				,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	17/06/1997
PCT/JP98/0	2613	3	15/06/1998		
International Pa C07D401/06	itent (Classification (IPC) or na	tional classification and IPC		
Applicant FUJISAWA	PHA	ARMACEUTICAL CO	D., LTD. et al.		i v Authority
This integrand is transfer	rnati ansm	onal preliminary exam nitted to the applicant	nination report has been pro according to Article 36.	epared by this Int	ernational Preliminary Examining Authority
		T consists of a total o	f 8 sheets, including this c	over sheet.	
☐ This	s rep	ort is also accompanio		ts of the descripti	on, claims and/or drawings which have rectifications made before this Authority the PCT).
These a	nne	xes consist of a total of	of sheets.		
3. This rep		contains indications re	elating to the following item	s:	
i i					t dudical applicability
"	×	Non-establishment o	f opinion with regard to nov	elty, inventive st	ep and industrial applicability
iv					
V	Ø	Danasad statement	t under Article 35(2) with re ations suporting such state	gard to noverty, I ment	nventive step or industrial applicability;
VI	\boxtimes	Certain documents	cited		
VII	X	Certain defects in the	e international application	ation	
VIII		Certain observations	on the international applic		
	_			Date of completio	n of this report
		on of the demand			03. 03. 99
02/12/19			·	Authorized office	STEED ES MICHICAL
Name and preliminary	ехал	ng address of the internat nining authority: ropean Patent Office	onas		A STANLING OF THE STANLING OF
	n 6	oogge Munich	ooss annu d	Hartrampf, G	Tangara salah sala
	Te Fa	1. (+49-89) 2399-0 Tx: 52 x: (+49-89) 2399-4465	23000 врим ч	Telephone No. (-	+49-89) 2399

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP98/02613

I.	Bas	is of the report	
1.	resp	onse to an invitation	rawn on the basis of (substitute sheets which have been furnished to the receiving Office in on under Article 14 are referred to in this report as "originally filed" and are not annexed to o not contain amendments.):
	Des	cription, pages:	
	1-18	30	as originally filed
	Clai	ms, No.:	
	1-10)	as originally filed
2.	The	amendments have	resulted in the cancellation of:
		the description,	pages:
		the claims,	Nos.:
		the drawings,	sheets:
3.		This report has be considered to go b	en established as if (some of) the amendments had not been made, since they have been beyond the disclosure as filed (Rule 70.2(c)):
4.	Ado	litional observation	s, if necessary:
111	. Noi	n-establishment o	f opinion with regard to novelty, inventive step and industrial applicability
TI OI	to b	estions whether the industrially applic	e claimed invention appears to be novel, to involve an inventive step (to be non-obvious), able have not been examined in respect of:
		the entire internat	ional application.
	×	claims Nos. 8.	
b	ecau	se:	
		the said internation	nal application, or the said claims Nos. relate to the following subject matter which does emational preliminary examination (specify):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP98/02613

		the description, claims o that no meaningful opinion	r drawir on could	ngs (<i>indic</i> d be form	ate particular elements below) or said claims Nos. are so unclear ed (specify):
		the claims, or said claim could be formed.	s Nos.	are so in	adequately supported by the description that no meaningful opinion
	×	no international search r	eport h	as been e	established for the said claims Nos. 8.
٧.	Rea app	soned statement under dicability; citations and	· Article explan	35(2) w ations sı	ith regard to novelty, inventive step or industrial apporting such statement
1.	Sta	tement			
	Nov	velty (N)	Yes: No:	Claims Claims	4 1-3,5-10
	Inve	entive step (IS)	Yes: No:	Claims Claims	1-10
	Ind	ustrial applicability (IA)	Yes: No:	Claims Claims	1-7,9,10
2.	Cita	ations and explanations			
	see	separate sheet			
VI	. Ce	rtain documents cited			
1.	Се	rtain published document	s (Rule	70.10)	
	and	i/or			
2.	No	n-written disclosures (Rul	le 70.9)		

see separate sheet

INTERNATIONAL PRELIMINARY **EXAMINATION REPORT**

International application No. PCT/JP98/02613

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

ad section III

For the assessment of the present claim 8 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

ad section V

1. PRIOR ART

The following documents cited in the International search report were taken into consideration

consideration PRIG EP 0 655 442 A (D1)— 5/31/1995 WO 96 34864 A (D2) WO 96 37489 A (D3) WO 97 08166 A (D4).

2. NOVELTY

With regard to the prior art documents cited above the subject-matter claimed, i.e. aroyl-piperazine derivatives according to the formula in claim 1, does **not** appear to fulfil the requirements of novelty, cf. Article 33(2) PCT.

There exist several overlaps of the present compounds with those disclosed in documents D1 to D4.

EXAMINATION REPORT - SEPARATE SHEET

3

(i) The compounds of formula (I) in D1 wherein (D1 nomenclature) X is CO, R² is (un)substituted aryl or (un)substituted aromatic heterobicyclic group, R⁴ is -A-(Z)_p, A is a bond, alkylene, alkenylene or alkynylene, Z is (un)substituted aromatic hetero(mono- or bi-)cyclic group and in particular those of table 1, see esp. examples 50-44 and 50-48 are covered by present claims 1-3, 5-7, 9 and 10.

(V)

(ii) The compounds of formula (I) in D2 wherein (D2 nomenclature) Ar₁ is (un)substituted phenyl or naphthyl, X is O, I is zero, n is 1, Ar₂ is (un)substituted heteroaryl, phenyl or naphthyl, R₂ is hydrogen or alkyl, X is (H,H) and Z is one of these heterocyclicimino groups are covered by present claims 1, 2, 6, 7, 9 and 10.



(iii) The compounds of claims 1 and 8 in D3 are covered by present claims 1, 5-7, 9 and 10.



(iv) The compounds of formula (I) in D4 wherein (D4 nomenclature) Ar₁ is (un)substituted phenyl or naphthyl, X is O, I is zero, n is 1, Ar₂ is (un)substituted heteroaryl, phenyl or naphthyl, R₂ is hydrogen or alkyl, X is (H,H) and Z is substituted piperidinylimino are covered by present claims 1, 6, 7, 9 and 10.

Thus at present claims 1-3 and 5-10 <u>cannot</u> be considered to be novel. The Applicant is invited to remove any overlap existing between the present application and the disclosures of the prior art. As a precautionary measure it is pointed out to the Applicant that the disclosure in a prior document likely to affect the novelty of a claim is not necessarily limited to the specific working examples but also comprises any reproducible technical teaching described in the document.

3. INVENTIVE STEP

3.1. The present application is directed to aroyl-piperazine derivatives which are neurokinin antagonists.

From the prior art available so far the following is known. Documents D1 to D4 disclose already aroyl-piperazine derivatives which are (at least partially) identical to the present compounds. These compounds are additionally neurokinin

EXAMINATION REPORT - SEPARATE SHEET

antagonists thus exhibiting the same properties as the compounds presently claimed.

3.2. In order to establish an inventive step in the sense of Article 33(3) PCT, it appears to be necessary to restrict the claims to compound(group)s that represent a reasonable generalisation of the examples given, that is, for which it can be made credible that they indeed possess the alleged properties. It should be borne in mind that a technical effect which justifies the selection of the claimed compounds must be one which can be fairly assumed to be produced by substantially all the selected compounds.

Due to lack of any experimental test data and/or pharmacological data which could be related to single compounds and/or convincing arguments it is for the time being not clearly evident that the problem has actually been solved.

4. INDUSTRIAL APPLICABILITY

Insofar the presently claimed compounds exhibit said pharmaceutical properties no objection arises, cf. Article 33(4) PCT.

Claim 8 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim, cf. Article 34(4)(a)(i) PCT.

ad section VI

WO 97 22597 A

18.12.95

12.12.96

26.06.97

16.05.96

30.09.96

NTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SI		International application No. IEET	PC1/JP98/02613	
WO 98 08826 A	30.08.96	28.08.97	5.03.98	
WO 98 18788 A	30.10.96	28.10.97	7.05.98	

The priority documents pertaining to the present application were not available at the time of establishing this international preliminary examination report. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the P-documents cited in the international search report could become relevant to assess whether the claims satisfy the criteria set forth in Article 33(1) PCT.

ad section VII

 To meet the requirements of Rule 5.1(a) PCT, all of the documents cited in the International search report should have been identified in the description and the relevant background art disclosed therein should have been briefly discussed.

INTERNATIONAL SEARCH REPORT

nts | chai Application No

POT/JP 98/02613

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/06 A61K31

C07D413/06

C07D401/06 A C07D403/14 C

Ä61K31/495 C07D401/12 C07D241/04 A61K31/535 A61K31/55 C07D413/12 C07D401/14 A61K31/54 C07D407/06 C07D403/06 C07D417/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 CO7D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
х	EP 0 655 442 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 31 May 1995 cited in the application see claims 1-3,6-8; examples 50-44,50-48; table 1	1-3,5-7, 9,10
X	WO 96 34864 A (SCHERING CORPORATION) 7 November 1996 see claims 1,2,4-8.10,22-24	1,2,6,7, 9,10
X	WO 96 37489 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 28 November 1996 see claims 1-7	1,5-7,9, 10
X	WO 97 08166 A (SCHERING CORPORATION) 6 March 1997 see claims 1-3,5,12-14	1,6,7,9, 10

Y Further documents are listed in the continuation of box C.

X Patent family members are listed in annex.

- Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of theinternational search

Fax: (+31-70) 340-3016

Date of mailing of the international search report

21 September 1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2

NL - 2280 HV Rijswijk

Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.

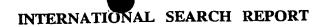
Authorized officer

Hartrampf, G

Form PCT/ISA/210 (second sheet) (July 1992)

page 1 of 2

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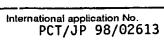




707/07 93/02613

	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	Relevant to claim No.
Category '	Citation of document, with indication where appropriate, of the relevant passages	nelevant to Gaim No.
ο, χ	WO 97 22597 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 26 June 1997 cited in the application see examples 45,50-52,56,58-60,63,67,70,77,85,86 see claims 1-7,9-14	1-3,5-7, 9,10
Ρ, Χ	WO 98 08826 A (SCHERING CORPORATION) 5 March 1998 see claims 1,2,4,12-14	1,2,6,7, 9,10
Ρ,Χ	WO 98 18788 A (SCHERING CORPORATION) 7 May 1998 see claims 1-4,12-16 	1,2,6,7, 9,10
	·	
	·	

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INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of hist sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: 8 because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

prormation on patent family members.

Patent document cited in search repor	t	Publication date		atent family nember(s)	Publication date
EP 0655442	A	31-05-1995	AU AU CA CN HU JP US ZA BR	689504 B 7911194 A 2136712 A 1107149 A 71348 A 7242641 A 5670505 A 9409228 A 9500539 A	02-04-1998 08-06-1995 30-05-1995 23-08-1995 28-11-1995 19-09-1995 23-09-1997 01-08-1995 31-10-1995
WO 9634864	A	07-11-1996	US AU CA CZ EP NO PL US US AU EP WO NO PL	5719156 A 5714196 A 2218887 A 9703423 A 0823906 A 975028 A 323235 A 5798359 A 5795894 A 6997996 A 0850236 A 9708166 A 980848 A 325339 A	17-02-1998 21-11-1996 07-11-1996 18-03-1998 18-02-1998 30-12-1997 16-03-1998 25-08-1998 18-08-1998 19-03-1997 01-07-1998 06-03-1997 30-04-1998 20-07-1998
WO 9637489	Α	28-11-1996	AU EP ZA	5703196 A 0846116 A 9604101 A	11-12-1996 10-06-1998 29-07-1996
WO 9708166	A	06-03-1997	US AU EP NO PL AU EP NO CA CZ PL	5795894 A 6997996 A 0850236 A 980848 A 325339 A 5714196 A 0823906 A 975028 A 2218887 A 9703423 A 323235 A	18-08-1998 19-03-1997 01-07-1998 30-04-1998 20-07-1998 21-11-1996 18-02-1998 30-12-1997 07-11-1996 18-03-1998 16-03-1998

INTERNATIONAL SEARCH REPORT

information on patent family memoers

inte chai Application No PCT/JP 98/02613

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9708166	Α		WO 96	9634864 A	07-11-1996
WO 9722597	Α	26-06-1997	AU	1110697 A	14-07-1997
WO 9808826	Α	05-03-1998	AU	4080097 A	19-03-1998
WO 9818788	Α	07-05-1998	AU	4991797 A	22-05-1998